Application Reviews by RFA/Genomics/GC1R-06683

REVIEW REPORT FOR CIRM RFA 12-06R GENOMICS CENTERS OF EXCELLENCE AWARDS (R)

GC1R-06683: Center for Population and Functional Genomics in Stem Cell Biology and Regenerative Medicine

GWG Overall Center Recommendation: Tier 2
GWG Overall Final Score: 70

GWG Data Center Recommendation: Tier 3
GWG Data Center Final Score: 63

CIRM Staff Recommendation: Do not fund

Public Abstract (provided by applicant)
Genomics describes a branch of biology that seeks to understand the relationship between the DNA of many people and traits those people have. If person A and person B are not identical twins they'll have many small differences in their DNAs. If person A gets a disease and person B does not, it could be due to one or more of these differences, and that's what genomics seeks to try to determine. This Stem Cell Genomics Center of Excellence uses robotic tools and computers to test many combinations of differences in stem cells from humans to develop or improve human therapies. This Center tries to accomplish this by characterizing differences in protein expression signals - instructions for traits that come from a person's DNA - in cancer-related stem cells and hematopoietic stem cells for example. The hope is that in so doing the Center can find differences that explain why, for example, stem cell responses to drugs differ so profoundly both between individuals and even within them. Given the quality and number of excellent California researchers in the stem cell field, the Center also opens its doors to collaboration for other stem cell and regenerative medicine research projects.

Statement of Benefit to California (provided by applicant)
[Redacted] was founded [Redacted] and is centered within a biomedical research hub [Redacted]. Since its inception, [Redacted] has adopted a singular vision to drive new biological insight and accelerate the pace of drug discovery through the creative application of technology and co-located, multidisciplinary expertise. In this regard, [Redacted] has brought together over 450 experts that provide a breadth of capabilities across genomics, biology, informatics, engineering and chemistry that work collaboratively to discover innovative medicines that address unmet medical need. To accomplish this mission, [Redacted] has extensively collaborated with world-renowned research institutions throughout CA and the proposed Stem Cell Center of Excellence seeks to further expand these research ties. To this end, [Redacted] will specifically dedicate over one-third of the total award to leverage our extensive expertise, cutting-edge technologies, data management and drug-discovery infrastructure to advance CA-based research investigator objectives and provide resulting data freely to the scientific community. We firmly believe that our unique infrastructure and history of executing successful collaborations with CA institutions will provide an incomparable environment to catalyze the pursuit of critical, transformative, translational and data intensive genomics research in the areas of stem cell biology, regenerative medicine and genomics.

Review Summary
This application describes a Genomics Center involving collaboration between two academic institutions and one industry partner. The proposal includes three Center-Initiated Projects (CIPs), a Collaborative Research program, and a Data Coordination and Management Center.

Center Organization and Operational Plan
- Reviewers were enthusiastic about the organizational plan; the staff hierarchy is well presented and reflects an appropriate approach to managing this project.

- Reviewers appreciated the strong institutional commitment, which includes covering the salaries of listed personnel.

- This application is led by a good group of interactive collaborators with a strong track record in science and in collaborating with other academic centers.

Collaborative Research Projects

- Overall, reviewers judged this collaborative research plan to be well written and well thought-out. They had confidence in its successful execution, especially since leadership has extensive experience with managing many different projects.

- Reviewers praised the proposed mechanism of guidance and mentorship for external collaborators and felt that administrative issues of collaborative projects were appropriately addressed.

- Reviewers appreciated that the group responded well to the previous review's comments.

- Reviewers observed that the proposed collaborative activities are diverse and demanding, requiring the mobilization of many different tools and capabilities. They questioned whether this team is prepared to thoroughly implement all proposed elements for collaborative projects.

- Important details concerning the generation and delivery of genomics data in collaborative projects were lacking.

CIP-1

The focus of this CIP is the analysis of data generated in CIP-2 and CIP-3 to define key genes or gene networks that regulate the biology of stem cells. The applicants will analyze data from large sample collections using computational methods to integrate information about genomic variation, gene expression status and cellular characteristics (molecular population genetics).

- Although reviewers regarded the goals of this project to be significant in that they will provide important and innovative data analyses to CIP-2 and CIP-3, they strongly criticized that it is not a stand alone, separate project. This is not a scientific project but instead a core service to the other CIPs.

- The computational analyses are focused on identifying important relationships between genomic variation, gene expression status and cellular characteristics but reviewers felt that the applicants missed the opportunity to also include the contribution of epigenetics and higher-order genome organization in their assessments.

- The PI for CIP-1 is a very experienced investigator with a strong track record as a scientist and group leader.

CIP-2

For high risk subtypes of medullablastoma (MB), a malignant pediatric brain tumor, the mutations that drive the tumor are unknown. The goal of this CIP is to identify key driver gene networks for those MB subtypes through computational analyses of MB genomic datasets. The candidate drivers will then be functionally validated in induced pluripotent stem cell (iPSC)-derived neural progenitors, both in vitro and following transplantation into a mouse model in vivo. The anticipated outcome from this work is a greater understanding of the genetic events that determine poor outcome in MB patients.

- CIP-2 addresses a significant medical problem with a novel hypothesis and an innovative approach.

- Aim 1 is well within the capabilities of the team, but since much of the analysis has already been accomplished, reviewers were unclear how many more MB datasets need to be analyzed, a question not addressed in the proposal.

- Since no definitive evidence is provided showing that the proposed iPSC-derived neural progenitor model recapitulates MB, reviewers had strong doubts that the proposed validation studies in Aims 2 and 3 will be informative for MB biology.

- Reviewers regarded the focus on gene expression signatures to characterize driver mutations as innovative. But, the proposal would have been greatly improved by a demonstration that forced expression of a known driver gene alters gene expression as anticipated.

- In contrast to the applicants' claim, reviewers doubted that the proposed studies would identify the true cells of origin for MB, and further criticized that the tumor biology lacked stem cell focus.

- Key preliminary data and conclusions are referred to as personal communications or mentioned but not provided. For instance, the comparison of genes with significance to MB subtypes lacks specifics, precluding an assessment of the status of this research.

- Reviewers criticized the lack of key details in experimental design. For instance, no information is provided as to whether, and, if so, how prioritization of candidate drivers will be conducted, how the secretome will be analyzed, or how patient samples will be acquired and handled for culture. In vitro tumorigenesis is inadequately addressed.

- The research team is superb and possesses a substantial strength in systems biology and also has access to a large set of clinical specimens and to relevant animal models.

CIP-3
The ex vivo expansion of hematopoietic stem cells (HSCs) in cord blood (CB) units has utility for HSC transplantation and is currently under clinical investigation. However, substantial variation exists amongst CB units in their HSC expansion and engraftment potential. Based on the hypothesis that natural human genetic variation is responsible for this variability, the applicants intend to employ a systems genetics approach (establish associations between genomic data and HSC potential from large numbers of CB units) to define the regulatory pathways that control HSC biology. It is hoped that once identified, these pathways will provide novel targets to improve HSC expansion and transplantation.

- Reviewers judged the proposed studies to be based on an intriguing and somewhat novel hypothesis, and appreciated that this CIP explores the fundamental biological question as to why some HSC preparations engraft and others do not. Reviewers pointed out that in addition to the genetics of the CB unit, part of the variability in HSC engraftment stems from variability in host-graft interactions and, in cases of double CB transplant, also in graft-graft interactions.

- While this project addresses an interesting biological question, the potential clinical impact of the proposed studies was debated. Although some reviewers were enthusiastic, others were skeptical whether improving HSC expansion methods alone would result in an increase of CB transplantation, since one of the main clinical problems is lack of rapid, short-term engraftment, which is not necessarily due to low HSC numbers.

- Reviewers agreed with the applicants that a more reliable HSC engraftment model than currently in use is necessary in order to be able to extract meaningful information from this project. Some reviewers lacked confidence that the proposed solution, although based on a reasonable approach, will yield a reliable, quantitative test method, while others felt that the HSC engraftment model could work reliably.

- Reviewers were enthusiastic about the team's previous success with ex vivo manipulation of CB units, but felt that preliminary data supporting the feasibility of the proposed systems genetics approach were not strong.

- Reviewers pointed to some shortcomings in experimental design, e.g. they criticized that the human clinical trial and the proposed analyses in the animal model measure distinct outcomes that reflect different attributes of CB transplant biology and that power calculations to justify the scope of the project were not provided.

- Reviewers praised the team as a whole as being ideally suited for this type of study. The Principal Investigator (PI) and team were instrumental in laying important groundwork for this proposal, but reviewers noted that the PI has limited experience with the proposed genome-wide analyses.

Data Coordination and Management
- Reviewers criticized the emphasis placed on establishing a secure web interface for clinical data and a legal framework. Though these activities have their role in a robust genome center, details for how genomic data will be handled were too sparse, thus making it impossible to critically evaluate the priority needs for Data Coordination and Management (DCM).

- Reviewers observed that aspects of data handling are focused on handling patient data and were very concerned that the proposed platform was not adequately designed to handle high throughput genomics data.

- The budget lacked detail, precluding assessment how the team distributes effort and expenses, and if this team would be able to optimally interface with critical expertise and resources at a collaborating institution.

- Reviewers thought the leadership team has much of the necessary expertise for managing a DCM Center.

- The plans for outreach to and coordination with a second CIRM Genomics Center, if necessary, was deemed adequate.

Source URL: https://www.cirm.ca.gov/our-funding/application-reviews-rfagenomicsgc1r-06683